

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Gopi M. Venkatesh et al.

Application No.: 10/713,929

Confirmation No.: 4820

Filed: November 14, 2003

Group Art Unit: 1615

For: MODIFIED RELEASE DOSAGE FORMS OF
SKELETAL MUSCLE RELAXANTS

Examiner: BARHAM, Bethany P.

DECLARATION UNDER 37 C.F.R. § 1.131

I, Dr. Gopi Venkatesh declare as follows:

1. I am a named inventor of the above-noted application (Ser. No. 10/713,929)
2. I have read and understood the Official Action of January 11, 2008, and in particular the rejection of the pending claims under 35 U.S.C. §103 over the combination of U.S. Publ. No. 2004/0197407 (the '407 application) and U.S. Publ. Nos. 2003/0215496 or 2003/0099711.
3. I understand that the earliest asserted priority date of the '407 application is February 11, 2003, through the priority claim to U.S. Provisional Application Ser. No. 60/446,425.
4. The subject matter of the pending claims of the present application was invented by Gopi Venkatesh and James M. Clevenger (the named inventors) prior to February 11, 2003.
5. Example 3 of the instant application describes the formulation and production of a multiparticulate dosage form of cyclobenzaprine, wherein the cyclobenzaprine is coated on sugar spheres and covered with a water insoluble polymer to produced extended release beads (see paragraph 0045). Figure 4 of the instant application shows the release rate of the finished beads of Example 3 (e.g., **Batch 805-AAA-105**).

6. Exhibit A, dated before February 11, 2003, shows a "Master Formula" sheet documenting the production of the intermediate cyclobenzaprine coated beads used to make **Batch 805-AAA-105**. This intermediate batch (designated **Lot No. 837-AG-034**) comprises:

- "Sugar Spheres" (5475 g) coated with "cyclobenzaprine HCl" (1875 g) from "Acetone, NF 50/50% Ratio" and "USP Purified Water, 50/50% Ratio";
- seal coated with "2.00"% of "Opadry Clear YS-1-7006".

Exhibit B, dated before February 11, 2003, shows a "Master Formula" sheet documenting the actual production of **Batch 805-AAA-105** by coating the intermediate cyclobenzaprine beads of **Lot No. 837-AG-034** with an extended release water insoluble polymer:

- ER coating of **Lot No. 837-AG-034** with "Ethylcellulose 10P Premium (10 cps)" (363.6 g) and "Diethyl Phthalate" (36.4 g) dissolved in "Acetone, NF (98 parts)" and "USP Purified Water (2 parts)". Samples were collected with a coating weight of "10%" (designated **Batch or Lot No. 805-AAA-105**).

Exhibit C, dated before February 11, 2003, shows data for the mean cumulative release rate of cyclobenzaprine over time for "Lot # 805-AAA-105-10" (i.e., 10 wt.% ER coating, Batch 805-AAA-105). The data are identical to that presented in graphical form for the sample designated "10% ER Coating Wt., Batch 805AAA105" in Figure 4 of the instant application and shows that the 10% ER coated beads exhibit a release profile that after 2 hours, no more than about 40% of the total active is released; after 4 hours, from about 40-65% of the total active is released; after 8 hours, from about 60-85% of the total active is released; and after 12 hours, from about 75- 85% of the total active is released, wherein said dosage form is dissolution tested using United States Pharmacopoeia Apparatus 2 (paddles @ 50 rpm) in 900 mL of 0.1N HCl at 37°C. This is the same dissolution profile required by the pending claims.

7. Exhibit D, dated before February 11, 2003, is a batch record showing the ingredients of "Cyclobenzaprine HCl ER Beads", **Lot No. PE271EA001**:

- “Cyclobenzaprine HCl Intermediate Beads”, Item code **PE249**; coated with “Ethylcellulose” and “Diethyl Phthalate”.

Exhibit E, dated before February 11, 2003, documents the manufacture of “Cyclobenzaprine HCl MR Capsules, 30 mg”, **Lot No. PF306EA001**:

- “White, Opaque Hard Gelatin Capsules, Size 4”, filled with “Cyclobenzaprine HCl Extended Release Beads”, Item code **PE271**.

Exhibit F, dated before February 11, 2003, shows data for the mean cumulative release rate of cyclobenzaprine over time for clinical batch “Lot # PF306EA001”. The data are identical to that presented in graphical form for the clinical sample designated “PF306EA001” in Figure 6, Examples 4 and 5 of the instant application. Formulation PF306EA001 shows a release profile that after 2 hours, no more than about 40% of the total active is released; after 4 hours, from about 40-65% of the total active is released; after 8 hours, from about 60-85% of the total active is released; and after 12 hours, from about 75- 85% of the total active is released, wherein said dosage form is dissolution tested using United States Pharmacopoeia Apparatus 2 (paddles @ 50 rpm) in 900 mL of 0.1N HCl at 37°C. This is the same dissolution profile required by the pending claims.

8. Thus, Exhibits A and B document the production of the identical multi-particulate cyclobenzaprine dosage forms described in Example 3 of the present application, and as set forth in the instant claims, before February 11, 2003.

9. Thus, Exhibits D and E document the production of the identical clinical batch described in Examples 4 and 5 of the present application, and as set forth in the instant claims, before February 11, 2003.

10. I further declare that all statements made herein on my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code, and that

such willful false statements may jeopardize the validity of the above-referenced application or any patent issuing thereon.

Respectfully submitted,

G. M. Venkatesh

Gopi Venkatesh

1/30/08

Date

Exhibit A

Master Formula

Page 1 of 1

Product Name: Cyclobenzaprine HCl, Drug Layered Beads		Batch Number: 837A034		Date: <u> </u>	
Physical Description: Off White		Capsule Size: N/A		Batch Size: 7500.0 gms	
Imprint (Uppers): N/A		Imprint (Lowers): N/A		Unit Weight (mg): N/A	
Written By: A.Gallo <i>M. Gallo</i>		Reviewed By: <u> </u>		Time: 7:20 AM	

ITEM #	Ingredients (Trade Name Grade)	Raw Material Lot #	Quantity		Quantity		Quantity		Weighted		Checked		Date Weighed
			%	Mg/Unit	Gm/batch	Weighted	By	By	By				
1	*Cyclobenzaprine HCl	C14607401	25.00	7.50	1875.0 gm	1875.0							
2	Sugar Spheres 20 - 25 Mesh (Hansen)	RD - 9911114	73.00	21.90	5475.0 gm	5475.0							
3	**Opadry Clear YS - 1 - 7006	H10507376	2.00	0.60	150.0 gm	150.0							
4													
5													
6													
7													
8													
9													
10	Acetone, NF 50/50 % Ratio	A10707332			2812.50 ml	2812.50							
11	USP Purified Water, 50/50 % Ratio	W-10002061B			2812.50 ml	2812.50							
12	USP Purified Water @ 10.0 % of Seal Coat	W-10002061B			1350.0 ml	1350.0							
	Total:		100.00	30.00	7500.0 gm	7500.0							

Objective: to evaluate dose @ 25.0 % Using GPCG S

Note: Acetone, NF / USP Purified Water 50/50 Ratio.

* Item #10,11, 12 is use to make coating solutions. Both mg/ unit and g/ batch totals do not reflect entries.

TITLE CYCLOBENZAPRINE HCl EC BEADSBook No. 805From Page No. 104

Purpose: To EC coat Cyclobenzaprine HCl drug layered beads using solvent (50:50) Acetone : H₂O as a media. The drug layered beads were then Ethyl Cellulose coated using Acetone : H₂O (98:2). The EC was done using Glatt GPCG-5 Wurster.

Master Formula

Page 1 of 1

Product Name: Cyclobenzaprine HCl - Extended Release Beads (25.0 mg)									
Physical Description : Extended Release Coating									
Lot # 805-AAA-105									
Date : _____									
ITEM #	Ingredients (Trade Name Grade)	Raw Material Lot #	Quantity % W / W	Quantity Mg / Unit	Quantity Gm / batch	Quantity Weighted	Weighted By	Checked By	
1.	Cyclobenzaprine HCl, Drug Layered Beads	837-AG-034	3600.0			3600.0	AAA		
2.	Ethylcellulose 10P Premium (10cps), NF	B11407226	363.6			364.0	AAA		
3.	Diethyl Phthalate, USP	D11807500	36.4			36.4	AAA		
10.	Acetone, NF (98 parts)	A10707332	5639.0			5639.0	AAA		
11.	Purified Water, USP (2 parts)	W100-01	115.0			115.0	AAA		
Total:									
Objective: Evaluating Dose @ 10.0 % Samples were taken @ 7, 8, 9, & 10% of EC applied.									

AAA

To Page No

Witnessed & Understood by me,

Date

Invented by

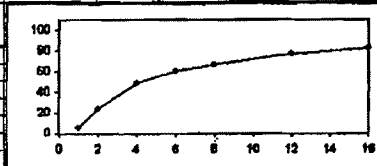
Anthony A. Agui

Date

TITLE Cyberbomazine HCLFrom Page No. 112

System Suitability Test Results			Reference: NB891.P104		Std 2 Conc. (mg/ml): 0.03043		Std 2 Dilution (ml): 1000		Actual Assay: 22.1	
Vessel	Weight (mg)	Active Wt (mg)								
1	140.85	31.15								
2	141.88	31.35								
3	142.03	31.39								
4	139.28	30.78								
5	141.04	31.17								
6	140.07	30.96								
Info	Area	Std Avg.	(%) Released	Avg. (%) Release	σ_{rel}	(%) RSD	Spec.	Pass/Fail		
Std 1	523879									
1.1	38087		6	6	0.5	9.1	FIO	FIO		
1.2	37241		6							
1.3	31848		5							
1.4	31505		5							
1.5	34893		6							
1.6	33750	(Std 1&2)	6							
Std 2	524333	524105								
2.1	149590		25	24	1.0	4.2	NMT 40%	PASS		
2.2	151986		25							
2.3	136393		23							
2.4	135882		23							
2.5	146873		25							
2.6	148717	(Std 2&3)	25							
Std 3	523832	523983								
3.1	291002		49	48	1.3	2.8	30% - 60%	PASS		
3.2	293085		49							
3.3	277113		46							
3.4	274632		47							
3.5	293105		49							
3.6	287012	(Std 3&4)	48							
Std 4	524819	524126								
4.1	363326		61	60	1.4	2.3	FIO	FIO		
4.2	364024		60							
4.3	351439		58							
4.4	340831		58							
4.5	364481		61							
4.6	358000	(Std 4&5)	60							
Std 5	526536	526579								
5.1	409548		68	67	1.5	2.3	60% - 90%	PASS		
5.2	410539		68							
5.3	395003		65							
5.4	387491		65							
5.5	408278		68							
5.6	403270	(Std 5&6)	68							
Std 6	526856	527698								
6.1	469068		78	77	1.2	1.5	FIO	FIO		
6.2	483710		77							
6.3	456293		78							
6.4	440242		75							
6.5	460754		76							
6.6	458822	(Std 6&7)	77							
Std 7	525680	526268								
7.1	504593		84	83	1.0	1.2	NLT 75%	PASS		
7.2	504335		84							
7.3	491652		82							
7.4	483535		82							
7.5	501954		84							
7.6	501349	(Std 7&8)	84							
Std 8	526741	526211								

Sample	Time	Avg. Refd (%)	RSD
S05-AAA-105-10	1.0	6	9.1
N/A	2.0	24	4.2
	4.0	48	2.6
	6.0	60	2.3
	8.0	67	2.3
	12.0	77	1.5
	16.0	83	1.2



For System Suit
See p. 114

$$\% \text{ Released} = \left(\frac{501349}{526579} \right) \left(\frac{0.03043 \text{ mg/ml}}{0.03043 \text{ mg/ml}} \right) \left(\frac{900 \text{ ml}}{1000 \text{ ml}} \right) \left(\frac{100}{100} \right)$$

$$= 84.3\%$$

$$= 84.3\%$$

Chromatograms stored in Box 891

To Page No. 112

Witnessed & Understood by me,

Don Henley

Date

[Signature]

Invented by

Recorded by

Y. K. K. K.

Date

[Signature]

ISSUED BY Q.A.

Eurand America, Inc.
Cyclobenzaprine HCl MR Capsules, 30 mg
Batch Size – 130,000 Capsules (Theoretical))
MF#: A-60PF306-A

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Lot # PF306EA 001		Date of Manufacturing: [REDACTED]	
Effective Date: [REDACTED]		Inc. 11/14 MANUF CE	
Prepared By: <i>James M. Chavez</i>	Date: [REDACTED]		
MFG. Approval By: <i>J. Dean</i>	Date: [REDACTED]		
R&D Approval By: <i>L.M. Venkatesh</i>	Date: [REDACTED]		
QA Approval By: <i>Thomas M. Purdy</i>	Date: [REDACTED]		
QA Issue: <i>Thomas M. Purdy</i>	Date: [REDACTED]		
QA Audited By: <i>Thomas M. Purdy</i>	Date: [REDACTED]		

Item Code	Item No.	mg per capsule	% per Capsule (w/w)	Ingredient Name	Quantity per Batch
G134	1	37.00 ¹	21.91	White, Opaque Hard Gelatin Capsules, Size 4,	4.81 kg
PE271	2	131.87 ²	78.09	Cyclobenzaprine HCl Extended Release Beads	17.14kg
Total		168.87			21.95 kg

¹Based on a theoretical empty capsule weight of 37.0 mg
²Equivalent to 30 mg of Cyclobenzaprine Hydrochloride (Beads based on a theoretical assay of 22.75%)

Exhibit D

ISSUED BY Q.A.

Eurand America, Inc.
Cyclobenzaprine HCl ER Beads
Batch Size: 85 kg (Theoretical)
MF #: A-50PE271-A

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Lot #: PE271EA001	Date of Manufacturing: [REDACTED]
Effective Date: [REDACTED]	
Prepared By: [Signature]	Date: [REDACTED]
Mfg. Approval By: [Signature]	Date: [REDACTED]
R&D Approval By: Phil Perel	Date: [REDACTED]
QA Approval By: Thomas J. Purdus	Date: [REDACTED]
QA Issue: [Signature]	Date: [REDACTED]
QA Audited By: Thomas J. Purdus	Date: [REDACTED]

Item No.	Item Code	Bead Dosage (mg/g)	% per Batch (w/w)	Ingredient Name	Theoretical Quantity Per Batch**
1	PE249	910.00	91.00	Cyclobenzaprine HCl Intermediate Beads	77.4 Kg
2	E114	81.25	8.13	Ethylcellulose, Premium Std 10cps	6.9 Kg
3	D118	8.75	0.88	Diethyl Phthalate, NF	0.75 Kg
4	A107	----	----	Acetone, NF*	116.7 Kg
5	W100	----	----	Purified Water, USP*	2.4 Kg
		1000.00	100.01	TOTAL=	85.0 Kg

*Removed from process during the drying process

**Actual batch is based on the actual quantity of the Intermediate Beads available for use. See page 2

Exhibit E

Exhibit F

Cyclobenzaprine 30mg MR Capsules Lot# PF306EA001

1 hour				Avg. STD	8 hour				Avg. STD
CHKSTD	262100	CHKSTD	256775	259438	CHKSTD	263363	CHKSTD	270750	267057
1	10845	7	14041		1	205685	7	220888	
2	5838	8	14416		2	215918	8	218836	
3	12708	9	0		3	216018	9	205793	
4	11645	10	14435		4	211804	10	219400	
5	11232	11	15293		5	220533	11	211189	
6	10460	12	13404		6	214893	12	222248	
CHKSTD	256775	CHKSTD	262386	259581	CHKSTD	270750	CHKSTD	263356	267053
2 hour					12 hour				
CHKSTD	262386	CHKSTD	263589	262988	CHKSTD	263356	CHKSTD	261737	262547
1	73230	7	83090		1	232004	7	247658	
2	80450	8	86176		2	245230	8	245567	
3	80522	9	81274		3	246103	9	230755	
4	77577	10	84345		4	245046	10	248980	
5	81204	11	78231		5	251589	11	237970	
6	80205	12	85540		6	244480	12	252555	
CHKSTD	263589	CHKSTD	262191	262890	CHKSTD	261737	CHKSTD	261590	261664
4 hour					16 hour				
CHKSTD	262191	CHKSTD	261515	261853	CHKSTD	261590	CHKSTD	261252	261421
1	135093	7	159208		1	247344	7	264019	
2	143494	8	158288		2	262134	8	262718	
3	145159	9	161618		3	263893	9	242544	
4	143021	10	159810		4	258831	10	265913	
5	146228	11	149087		5	268488	11	254822	
6	145149	12	160801		6	265056	12	269862	
CHKSTD	261515	CHKSTD	268598	265057	CHKSTD	261252	CHKSTD	262478	261864
8 hour					STD conc				
CHKSTD	268598	CHKSTD	266252	267425		0.03007	mg/ml		
1	182176	7	197178		Strength		30	mg	
2	191272	8	194590						
3	192435	9	186135						
4	187995	10	197029						
5	198802	11	186727						
6	190502	12	198623						
CHKSTD	266252	CHKSTD	263363	264808					
1 hour (FIO)					8 hour (80 - 90%)				
1	4	7	5		1	69	7	75	
2	2	8	5		2	73	8	74	
3	4	9	0		3	73	9	70	
4	4	10	5		4	72	10	74	
5	4	11	5		5	74	11	71	
6	4	12	5		6	73	12	75	
Average:	4 %				Average:	73 %			Pass
2 hour (8 - 40%)					12 hour (FIO)				
1	25	7	29		1	80	7	85	
2	28	8	30		2	84	8	85	
3	28	9	28		3	85	9	80	
4	27	10	29		4	84	10	86	
5	28	11	27		5	86	11	82	
6	28	12	29		6	84	12	87	
Average:	28 %			Pass	Average:	84 %			
4 hour (36 - 60%)					16 hour (NLT 75%)				
1	47	7	54		1	85	7	91	
2	49	8	54		2	90	8	91	
3	50	9	52		3	91	9	84	
4	49	10	54		4	89	10	92	
5	51	11	51		5	93	11	88	
6	50	12	55		6	91	12	93	
Average:	51 %			Pass	Average:	90 %			Pass
6 hour (FIO)									
1	61	7	67						
2	65	8	66						
3	65	9	63						
4	63	10	67						
5	67	11	64						
6	64	12	68						
Average:	65 %								